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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,010	05/01/2001	Perry A. Frey	032026-0476D	5359

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FOLEY & LARDNER LLP
150 EAST GILMAN STREET
P.O. BOX 1497
MADISON, WI 53701-1497

EXAMINER

HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

MAIL DATE	DELIVERY MODE
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05/11/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/847,010

Applicant(s)

FREY ET AL.

Examiner

Richard G. Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/23/2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 29,37,40-48 and 59-72 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 29,37 and 42-44 is/are allowed.
- 6) ☒ Claim(s) 40,41,45-48,59-61,63,65 and 67-72 is/are rejected.
- 7) ☒ Claim(s) 62,64 and 66 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's amendment of claims 40, 45-47 and 60 and the addition of claims 61-72, in the paper of 2/23/2007, are acknowledged. Claims 29, 37, 40-48, 59 and 61-72 are still at issue and are present for examination.

Applicants' arguments filed on 2/23/2007, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claim 62, 64 and 66 are objected to because of the following informalities: Claim 62 recites "wherein the lysine 2,3-aminomutase has SEQ ID NO: 4". It is suggested that this be amended to "wherein the lysine 2,3-aminomutase **has the amino acid sequence of** SEQ ID NO: 4".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40, 41, 45-48, 59-61, 33, 65, 71 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40, 41, 46-48, 59 and 60 are indefinite in that it is unclear as to what is encompassed by the referred to "conservative amino acid variant of SEQ ID NO: 4".

This rejection is discussed in the previous office action.

The rejection was previously stated as it applied to previous claims 40, 41, 46-48, 59 and 60. In response to this rejection applicants have amended claims 40 and 45-47 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection on the basis that applicant's specification at page 7, lines 9-29 discuss at length the meaning of "conservative amino acid variant". Applicants submit that consistent with the meaning known in the art, the phrase is described in general terms (e.g., "an alkyl amino acid ...for an alkyl amino acid, etc.). Applicants further submit that additionally applicants have amended the claims to recite "one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4", allowing the skilled artisan to determine exactly how many and what type of variants are permitted.

Applicant's amendment and traversal is acknowledged and has been carefully considered, however, is not found persuasive on the following basis. It remains that applicants claims continue to be drawn to those methods of producing L-b-lysine comprising the use of a lysine 2,3-aminomutase having an amino acid sequence of a "conservative amino acid variant of SEQ ID NO: 4" and while applicants appear to have limited the extent of conservative amino acid substitutions of SEQ ID NO: 4 that are allowed (i.e. 72%), it remains that the term "conservative amino acid variant" remains unclear. While applicants have presented various groups of changes that applicants

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might consider "conservative" (i.e. alkyl, aromatic, sulfur containing, hydroxyl-containing, acidic, basic, etc.) it remains what others if any might be also considered to be encompassed within the scope of "conservative". Further, such a term varies depending upon the person making such a determination. Thus it continues that the claims are indefinite in that it is unclear what specific amino acid substitutions are encompassed by the term "conservative amino acid variant".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 41, 45-48, 59, 60, 61, 63, 65 and 67-72 are rejected under 35

U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.\

The rejection was previously stated as it applied to previous claims 40, 41, 46-48, 59 and 60. In response to this rejection applicants have amended claims 40, 45-47 and added claims 61-72 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection on the basis that applicants submit that in view of the description in the application of conservative amino acid substitutions and the eight disclosed sequences of lysine 2,3-aminomutases, the person of ordinary skill in

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the art would recognize the inventors as being in possession of the claimed invention. Applicants submit that claims 40, 46 and 47 do not recite all variants of SEQ ID NO: 4; but include only those conservative amino acid variants having one or more amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4 and as noted the meaning of "conservative amino acid variant" will be clear to the skilled artisan.

Applicants further submit that the eight widely divergent sequences of lysine 2,3-aminomutases disclosed in the specification offer the skilled artisan a wealth of information on amino acid substitutions which are tolerated by the enzyme, as SEQ ID NO: 4 shares only 31% sequence homology with lysine 2,3-aminomutase from *Clostridia*.

Applicant's amendment of the claims and complete argument is acknowledged, and has been carefully considered, however continues to be found nonpersuasive for the reasons previously made of record and for those repeated herein.

As pointed out by applicants, applicants disclose eight different lysine 2,3-aminomutases from different species, however, it is noted that none of these species appear to be encompassed by the claimed sub-genus of those conservative variants having one or more conservative amino acid substitutions to about 72% sequence identity to *E. coli* lysine 2,3-aminomutases of SEQ ID NO: 4. Applicants have noted that the claimed lysine 2,3-aminomutases of SEQ ID NO: 4 has only 31% sequence homology to the clostridial lysine 2,3-aminomutase, thus even the reference clostridial lysine 2,3-aminomutase is not encompassed by the claimed sub-genus. Given the widely divergent nature of the disclosed lysine 2,3-aminomutases, applicants have not

adequately described those conservative variants (See also above 112 second paragraph rejection) having one or more amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4.

The specification, continues to only provide the representative species of methods of use of SEQ ID NO: 4, encompassed by these claims (See above discussion). There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these conservative variants by any identifying structural characteristics or properties, for which no predictability of function is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. It is further noted that claims 61, 63, 65, 69 and 72 which each require that the "conservative amino acid variant of SEQ ID NO: 4 has one amino acid substitution" are interpreted as "conservative amino acid variant of SEQ ID NO: 4 comprises one amino acid substitution" and thus are not interpreted as further limiting the "conservative variant of SEQ ID NO: 4 from which they depend.

Claims 40, 41, 45-48, 59 and 60-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

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inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added recitation in claims 40, 41, 45-48, 59 -66 and 71 which recites "having one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4" is not supported by applicants specification at the time of filing and is thus considered new matter. Applicant's discussion of support for the above amendment on page 11 of the response dated 2/23/2007, is acknowledged. Applicants reference to page 17, lines 14-23 of applicants specification as disclosing that the eight disclosed sequences have up to about 72% sequence identity with the clostridial enzyme and the fact that SEQ ID NO: 4 itself (the currently claimed amino acid sequence) has only about 31% (sequence identity) is also acknowledged and not found persuasive in supporting applicants claim to the sub-genus of methods of use of those lysine 2,3-aminomutases "having one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4".

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 40, 41, 45-48, 59, 60, 61, 63, 65 and 67-72, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing L- β -lysine comprising the use of the lysine 2,3-aminomutase having an amino acid sequence of SEQ ID NO: 4, does not reasonably provide

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enablement for any method of producing L- β -lysine comprising the use of any lysine 2,3-aminomutase having an amino acid sequence having one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was previously stated as it applied to previous claims 40, 41, 46-48, 59 and 60. In response to this rejection applicants have amended claims 40, 45-47 and added claims 61-72 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection on the basis that as discussed above applicants specification have provided copious guidance with respect to the nature of conservative amino acid substitutions and the tolerance of various position in the amino acid sequence of SEQ ID NO: 4 for such substitutions.

As above, applicants submit that the 31% homology of SEQ ID NO: 4 with the lysine 2,3-aminomutase from *Clostridia* demonstrates the extreme tolerance which this enzyme generally has towards amino acid substitutions at many positions.

Second applicants submit that it was well within the skill in the art at the time of filing to determine regions of SEQ ID NO: 4 which are most tolerant of modification based upon the disclosed sequences of eight lysine 2,3-aminomutases. Applicants support this position by submitting the declaration of Dr. Victoria Sutton, which shows the alignment of the disclosed sequences using standard techniques. Thus applicants

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submit that contrary to the assertion that the application fails to provide a rational and predictable scheme for modifying any amino acid residue of SEQ ID NO: 4, applicants submit that this alignment shows exactly which residues appear to be the most and least tolerant of substitution, for example positions 48-52, 54-58, 87-95, 140-152, 215-217, 267-270 and 373-382 have a low sequence identity indicating a tolerance for amino acid substitutions. Applicants submit that other residues are conserved and unlikely to tolerate even a conservative amino acid substitution (i.e. 124, 128, 129, 131 and 133). Finally applicants submit that these choices of amino acid substitution are not indefinite as they must be conservative substitutions to about 72% sequence identity to SEQ ID NO: 4 and applicants submit that applicants specification teaches what constitutes a conservative amino acid substitution.

Applicants submit that accordingly, the skilled artisan understands how to make amino acid substitutions in the polypeptide of SEQ ID NO: 4 and which of these are likely to be successful or unsuccessful and thus the claims are enabled.

Applicant's amendment of the claims and applicants complete traversal of the rejection is acknowledged and has been carefully considered, however, continues to be found nonpersuasive for the reasons previously made of record and repeated herein.

Claims 40, 41, 45-48, 59, 60, 61, 63, 65 and 67-72 continue to be so broad as to encompass any method of producing L- β -lysine comprising the use of any lysine 2,3-amino mutase having an amino acid sequence having any conservative variant of SEQ ID NO: 4 up to 72% sequence identity to SEQ ID NO: 4 (See also above 112 second paragraph rejection). It continues that the scope of the claims is not commensurate with

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the enablement provided by the disclosure with regard to the extremely large number of variants broadly encompassed by the claims.

As pointed out by applicants in their traversal, the 31% sequence homology of SEQ ID NO: 4, with the lysine 2,3-aminomutase from *Clostridia* demonstrates the tolerance this enzyme has towards amino acid substitutions at many positions, however, this degree of variability conversely provides little guidance as to preferred single substitutions. Such a degree of variability might suggest that the determining factors relative to amino acid substitutions occurs at a higher level (i.e. at the level of multiple neighboring amino acids or secondary or tertiary structure). Applicants have provided little discussion and or guidance as to what determining variables exist for such amino acid substitutions and thus applicants have provided little to guidance as to the multitude of variants encompassed by applicants claims. Applicants presented analysis has determined a subgenus of residues that may be more tolerant to amino acid substitutions, however, applicants have not given any guidance as to the direction of such amino acid substitutions beyond that they are "conservative" (See previous and above 112 second paragraph rejection). Given the various definitions of conservative amino acid substitutions and the number of such conservative mutations that may exist, one of skill in the art would not understand how to make the vast majority of variants of SEQ ID NO: 4 that are encompassed by the claims.

The claims continue to place minimal structural limits on the polypeptides used in the claimed methods. As was previously stated, the disclosure is limited to those

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methods of producing L- β -lysine comprising the use of the lysine 2,3-aminomutase having an amino acid sequence of SEQ ID NO: 4, encompassed by the current claims.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all conservative modifications and fragments of SEQ ID NO: 4, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the desired activity; (B) the general tolerance of SEQ ID NO: 4 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of SEQ ID NO: 4 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue

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experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having desired activity.

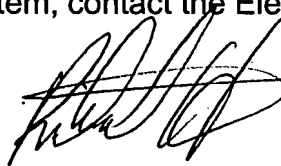
Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including those methods of use of conservative amino acid modifications of SEQ ID NO: 4, up to 72% sequence identity of SEQ ID NO: 4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those conservative variants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', written over a horizontal line.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rg
5/7/2007